Epidemiology of Brain Abscess

studies of incidence, risk factors, and prognosis

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STUDIES OF INCIDENCE, RISK FACTORS, AND PROGNOSIS

BY
JACOB BODILSEN

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EPIDEMIOLOGY OF BRAIN ABSCESS

STUDIES OF INCIDENCE, RISK FACTORS, AND PROGNOSIS

PhD thesis by

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CURRICULUM VITAE

Jacob Bodilsen was born in Farsø, Denmark, on March 27, 1980. He graduated from Secondary School in 2000 and started his medical studies at Aarhus University in 2001. Upon graduation in 2008, he completed an 18 month internship in North Denmark Region after which he worked for one year as a general practitioner in Brønnøysund, Norway. Next, he returned to Denmark in 2010 and worked as a resident at the Department of Infectious Diseases, Aalborg University Hospital (six months) and the Department of Internal Medicine, Farsø Hospital (six months). Following an inspiring five-month employment at the Department of Clinical Microbiology, he began his formal infectious diseases training at the Department of Infectious Diseases at Aalborg University Hospital (Professor Henrik Nielsen) in 2012. During his specialization, he spent 15 months at the Department of Internal Medicine at Sygehus Vendsyssel, Hjørring. In 2016, he completed a course in tropical medicine at Karolinska University Hospital in Stockholm, Sweden. He finished his training in infectious diseases in March 2017.

His first scientific work was a case report on Orf parapoxvirus infection in a Danish farmer in 2013. Under the guidance of Professors Henrik Nielsen and Henrik Schønheyder, he subsequently established a database of adults with community-acquired bacterial meningitis, which was used for several scientific publications. Together with Professor Henrik Nielsen, he co-founded the Danish Study Group of Infections of the Brain (DASGIB) in 2015. This is a nationwide scientific collaboration and prospective database of all patients with central nervous system infections in Denmark. He began his PhD project on the epidemiology of brain abscess in March 2017 at the Department of Infectious Diseases at Aalborg University Hospital (main supervisor Professor Henrik Nielsen) resulting in this thesis. He is currently working as a junior consultant at the Department of Infectious Diseases at Aalborg University Hospital. He is married to Karen Mariegaard and they have two girls, Selma and Sofia. Karen is now pregnant with their third child, expected to be born in April 2020.

ENGLISH SUMMARY

Brain abscess is a rare, but life-threatening infection. Epidemiological data on diseases remain the backbone for monitoring temporal changes and large-scale analyses of disease patterns in order to improve patient care. Current knowledge on the epidemiology and treatment of this serious condition relies almost exclusively on studies originating from departments of neurosurgery at tertiary care centres. Although informative on the clinical presentation of brain abscess, inherent limitations of such studies include selection bias and reduced generalisability. Moreover, most reports are hampered by short-term and incomplete follow-up, few are population-based or nationwide, and none provided control groups for analyses of risk factors or prognosis.

The aim of the thesis is to 1) review the anti-infective treatment of brain abscess, 2) assess the positive predictive value (PPV) of brain abscess diagnosis codes in the Danish National Patient Registry, 3) examine and quantify risk factors for brain abscess, 4) estimate trends in incidence and 1-year mortality of brain abscess patients, and 5) investigate the long-term risks of mortality and epilepsy in brain abscess patients.

This thesis is based on a narrative review and four epidemiological studies: a cross-sectional study, a case-control study, and two cohort studies. For the review, we conducted a literature search of the United States National Library of Medicine (Pubmed) database and consulted well-known textbooks of infectious diseases as well as studies included in a previously published systematic review of brain abscess. For the epidemiological studies, we took advantage of the unique civil registration number assigned to all Danish residents to individually link data from nationwide and population-based registries (*i.e.* Danish Civil Registration System, the Danish National Patient Registry, and the Danish Pathology Database), and the department of clinical microbiology at Aalborg University Hospital.

In study I, we confirmed that the preferred treatment regimen for community-acquired brain abscess in immuno-competent individuals should be a 3rd generation cephalosporin combined with metronidazole. However, these recommendations are based upon expert opinion and observational studies, and there is a need for prospective controlled studies to inform clinicians on the optimal anti-infective treatment of brain abscess. **In study II**, we found a crude PPV of 64% (95% CI 60-68) for brain abscess diagnosis codes among 695 patients identified in the Danish National Patient Registry from 2007 through 2016. However, if patients were required to either have both a diagnosis and surgical procedure code for brain abscess or to be admitted with a primary diagnosis code of brain abscess without newly diagnosed central nervous system cancer, spondylodiscitis/intraspinal abscess, or procedure code for subdural empyema, then the PPV increased to 84% (95% CI 80-87). **In study III**,

we included 1,384 first-time brain abscess patients and 13,839 population controls matched by age, sex, and municipality code. Well-known risk factors of brain abscess were quantified and several novel risk factors identified (*e.g.* immuno-modulatory treatments) with adjusted odds ratios ranging from 2-20. In addition, population attributable fractions showed that neurosurgery (12%), solid cancer (11%), ear-nose-throat infections (7%), and immuno-modulating treatments (5%) were substantial contributors to the burden of brain abscess on a societal level. **In study IV**, we observed a steady increase in the standardised incidence rate of brain abscess from 0.60 per 100,000 person-years during 1982-88 to 0.90 per 100,000 person-years during 2010-16. Increases in incidence were particularly notable among adults >40 years of age as well as in the proportion of brain abscess patients with immuno-compromise. The 30-day, 90-day, and 1-year mortalities were 7%, 13%, and 20% during 2010-16. Comparing mortality during 1982-88 with 2010-16 yielded an adjusted 1-year mortality rate ratio of 0.44 (95% CI 0.31-0.63). **In study V**, we compared the long-term prognosis of 1,384 brain abscess patients with 13,838 population controls matched by age, sex, and municipality code. We observed 1-year, 2-5 year, and 6-30 year hazard rate ratios of death of 17.5 (95% CI 13.9-22.0), 2.61 (2.16-3.16), and 1.94 (95% CI 1.62-2.31). The increased mortality was significant across sex and age groups except subjects >80 years of age, and remained consistent in both previously healthy and immuno-compromised individuals. The cumulative incidence of new-onset epilepsy was 32% in brain abscess patients compared with 2% in their matched population controls.

In conclusion, we substantiated current anti-infective treatment recommendations for brain abscess. However, evidence for these recommendations is sparse. We quantified known risk factors for brain abscess in addition to identification of several novel risk factors. The incidence of brain abscess is increasing and although the prognosis has improved during recent decades, 1-year mortality remains high and the lifetime risk of new-onset epilepsy is significant.

DANSK RESUMÉ

Hjerneabsces er en sjælden, men livstruende infektion. Epidemiologiske studier udgør hjørnestenen i overvågning af tidsmæssige variationer af sygdomme og kan bidrage med unik indsigt i sygdomsmønstre. Hidtidig viden om epidemiologiske forhold og behandlingen af hjerneabsces beror næsten udelukkende på studier udgående fra neurokirurgiske afdelinger på højt specialiserede sygehuse. Om end sådanne studier er nyttige vedrørende patienternes kliniske præsentation, er de også sårbare overfor selektions bias og har begrænset ekstern validitet. Yderligere har de fleste kun kort og ukomplet opfølgning af patienter, få er nationale eller befolkningsbaserede, og ingen af studierne inkluderer kontrolgrupper i analyser af risikofaktorer eller prognose.

Formålet med denne afhandling er derfor at øge den nuværende viden gennem 1) at opsummere eksisterende data om behandling af hjerneabsces, 2) at undersøge den positive prædiktive værdi (PPV) af diagnosekoder for hjerneabsces i Landspatientregisteret, 3) at belyse og kvantificere risikofaktorer for hjerneabsces, 4) at evaluere forekomst og 1-års dødeligheden af hjerneabsces, og 5) at undersøge langtidsrisikoen for død og epilepsi blandt patienter med hjerneabsces.

Denne afhandling bygger på et narrativt review, et tværsnitsstudie, et case-control studie og 2 kohortestudier. For at identificere relevante artikler til det narrative review, foretog vi en søgning i United States Library of Medicine (Pubmed) databasen og konsulterede kendte lærebøger såvel som referencer benyttet i et tidligere systematisk review. Til de register-baserede studier benyttede vi det unikke CPR-nummer i Danmark til at koble data på individniveau mellem diverse landsdækkende registre (Landspatientregisteret, CPR-registeret, og Dansk Patologi Register) samt Klinisk Mikrobiologisk Afdeling på Aalborg Universitetshospital.

I studie 1 bekræfter vi, at den foretrukne empiriske behandling af samfundserhvervet hjerneabsces hos immunkompetente patienter bør være et tredjegenerations cephalosporin kombineret med metronidazol. Dog er hidtidige retningslinjer baserede på observationelle studier og eksperters vurdering, hvorfor prospektive og kontrollerede studier er absolut nødvendige for at øge vores viden om behandlingen af hjerneabsces. **I studie II** fandt vi, at den PPV for diagnosekoder for hjerneabsces var 64% (95% CI 60-68) blandt 695 patienter identificeret i Landspatientregisteret fra 2007 til og med 2016. Dog kunne denne øges til 84% (95% CI 80-87), hvis vi kun inkluderede patienter med både en diagnose og procedure kode for hjerneabsces, eller kun inkluderede indlagte patienter med en primær diagnosekode for hjerneabsces uden samtidig nyligt diagnosticeret cancer i centralnervesystemet, spondylodiskitis/intraspinal absces eller subduralt empyem. **I studie III** inkluderede vi 1,384 hjerneabsces patienter og 13,839 befolkningskontroller matchet på køn, alder, og bopælskommune. Vi undersøgte og kvantificerede både kendte og nye risikofaktorer for hjerneabsces (f.eks. diverse immunmodulerende behandlinger) og

fandt justerede odds ratioer vekslende mellem 2-20. Yderligere analyser (population attributable fractions) viste, at neurokirurgi (12%), ikke-hæmatologisk cancer (11%), øre-næse-hals infektioner (7%) og immunmodulerende behandlinger (5%) bidrog væsentligt til forekomsten af hjerneabsces i Danmark. **I studie IV** observerede vi en stigning i den standardiserede incidens af hjerneabsces i Danmark fra 0.60 per 100,000 person-år i perioden 1982-88 til 0.90 per 100,000 person-år i perioden 2010-16. Stigningen i forekomsten var særligt udtalt blandt voksne >40 år og blandt andelen med hjerneabsces og nedsat immunforsvar. Herudover fandt vi en 30-dages, 90-dages samt 1-års dødelighed på henholdsvis 7%, 13% og 20% i perioden 2010-16. En sammenligning af starten af studieperioden (1982-88) og slutningen af studieperioden (2010-16) udmøntede sig en justeret 1-års mortalitets rate ratio på 0.44 (95% CI 0.31-0.63). **I studie V** sammenlignede vi langtidsoverlevelsen og risiko for nyopstået epilepsi blandt 1,384 hjerneabscespatienter og 13,838 befolkningskontroller matchet på køn, alder, og bopælskommune. Vi fandt en 1-års, 2-5 års og 6-30 års hazard rate ratio for død på henholdsvis 17.5 (95% CI 13.9-22.0), 2.61 (2.16-3.16) og 1.94 (95% CI 1.62-2.31). Den øgede dødelighed var signifikant på tværs af køn og aldersgrupper, fraset ældre >80 år, og viste sig ensartet betydningsfuld blandt både tidligere raske og immunkompromitterede individer. Den kumulerede incidens for nyopstået epilepsi var 32% blandt hjerneabsces patienter og 2% blandt deres matchede befolkningskontroller.

Sammenfattende viser vores studier, at den nuværende empiriske behandling af hjerneabsces er relevant, men svagt understøttet af kliniske studier. Endvidere bekræftes og kvantificeres kendte og nye risikofaktorer for hjerneabsces, og forekomsten af hjerneabsces vises at være højere end hidtil troet – og stigende. Om end dødeligheden for hjerneabsces er faldende gennem de seneste årtier, vedbliver 1-års dødeligheden at være betragtelig ligesom livstidsrisikoen for nyopstået epilepsi.

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I am profoundly grateful to a number of persons without whom this project would not have been possible. First, I would like to thank my supervisors. Henrik Nielsen for his infinite patience with my countless e-mails, ideas, and questions. Thank you for introducing me to research and being a tremendous inspiration as a clinician, leader, and scientist. Michael Dalager-Pedersen for teaching me scientific writing and sharing your outstanding epidemiological knowledge and insights with me on a day-to-day basis. Your friendship is invaluable to me. Matthijs C. Brouwer for kindly bearing with me at our first encounters when I was star-struck, but more importantly for helpful feedback throughout these projects spanning study designs to publication, and for welcoming me into your state-of-the-art research group. I cherish these experiences and look forward to continuing our collaborations in the years to come.

Special thanks also to Diederik van de Beek for his significant contribution to this project including assistance in design of studies and outstanding review of manuscripts. I would also like to thank Henrik C. Schønheyder for generous help and scientific collaborations throughout the years and for being the first to suggest, that I should consider conducting studies on the epidemiology of brain abscess. Thanks to Gunnar Lauge Nielsen for excellent teaching sessions during my stay at Farsø Hospital, which really sparked my interest in epidemiology.
I am indebted to my friends and colleagues at the Department of Infectious Diseases, Aalborg University Hospital and to Nicolai Kjærgaard for travelling around the country reading medical records of brain abscess patients. I wish to thank Jesper Smit, Rasmus Richelsen, Kristoffer Koch, Hans Linde Nielsen, and other members of the Aalborg Infection Research (AIR) group for great discussions, advice, and encouragement. I also owe thanks to all members of the Danish Study Group of Infections of the Brain (DASGIB) for an inspiring collaboration and specifically for assistance with the validation study. Thanks to Lars Omland for enthusiastically engaging in future scientific collaborations on the epidemiology of brain abscess.

I would also like to express my gratitude to my family and friends for invaluable everyday help and support. Most importantly, I owe the world to my pregnant wife and partner in life Karen and our daughters Selma and Sofia – for your unfaltering support, patience, and love.

Jacob Bodilsen
Aalborg, March 2020.

Studies included in this thesis

Study I
Bodilsen J, Brouwer MC, Nielsen H, van de Beek D. Anti-infective treatment of brain abscess. Expert Rev Anti Infect Ther 2018;16:565–78

Study II
Bodilsen J, Dalager-Pedersen M, Kjærgaard N, van de Beek D, Brouwer MC, Nielsen H. Positive predictive value of ICD-10 diagnosis codes for brain abscess in the Danish National Patient Registry. Clin Epidemiol. 2018;10:1503-1508

Study III
Bodilsen J, Dalager-Pedersen M, van de Beek D, Brouwer MC, Nielsen H. Risk Factors for Brain Abscess: A Nationwide, Population-Based, Nested Case-Control Study. Clin Infect Dis. 2019 Oct 23 [Epub ahead of print]

Study IV
Bodilsen J, Dalager-Pedersen M, van de Beek D, Brouwer MC, Nielsen H. Incidence and mortality of brain abscess in Denmark: a nationwide population-based study. Clin Microbiol Infect. 2020;26:95–100

Study V
Bodilsen J, Dalager-Pedersen M, van de Beek D, Brouwer MC, Nielsen H. Long-term mortality and epilepsy in patients after brain abscess: A nationwide population-based matched cohort study. Clin Infect Dis. 2019 Nov 27 [Epub ahead of print]

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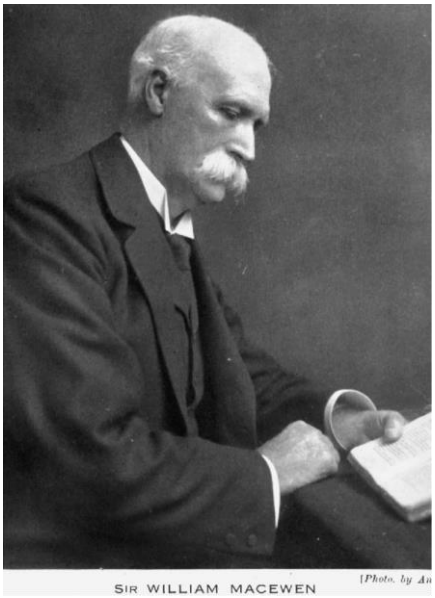
CHAPTER 1. INTRODUCTION

1.1. INTRODUCTION TO BRAIN ABSCESS

Brain abscess is defined as an encapsulated mass of bacteria, necrotic tissue, and leukocytes within the brain parenchyma. The infection has been considered uniformly lethal until the first published description of a patient successfully operated by French surgeon S. F. Morand in 1752[1]. Still, a review of published cases until 1872 concluded that only four of 214 surgically treated patients survived the infection[2]. The first real victory was accounted for in a landmark monograph by Sir William Macewen from Glasgow Royal Infirmary in 1893, in which the cure of 23 of 24 surgically treated brain abscess patients was described[3].



Portrait of Sir William Macewen adopted from Bowman, AK: The Life and Teachings of Sir William Macewen. A Chapter on the History of Surgery.[4]

The results were attributed to the Scotsman's profound knowledge of neuroanatomy, surgical skill, and adherence to the principles of aseptic surgery proposed by Joseph Lister[5], which at the time was controversial. Demonstrating a profound understanding of infectious diseases from an early stage, he emphasized the pivotal requirement of prompt treatment:

> "One might almost conclude that in uncomplicated abscesses of the brain operated on at a fairly early period, recovery ought to be the rule."[3]

Nonetheless, the overall mortality of brain abscess did not substantially improve until the introduction of antibiotic therapy into hospital care in the middle of the 20th century[6]. This was followed by further advances in the outcome of patients attributed to the implementation of computed tomography (CT) in the 1970s[7] and stereotactic guided neurosurgery in the 1980s[8,9].

1.2. PATHOGENESIS AND PATHOPHYSIOLOGY

Brain abscess occurs by invasion and encapsulation of bacteria, mycobacteria, or parasites within the brain parenchyma. The underlying mechanisms include cranial trauma with direct inoculation of bacteria into the brain, extension of infection from an adjacent cranial focus, and metastatic bacteraemic seeding from a distant source of infection. The predisposing condition of brain abscess remains unknown in about 19% of patients[10].

A landmark experimental study on the histologic evolution of brain abscess in dogs showed that the disease develops in four stages[11]:

1. Early cerebritis stage (days 1-3)
2. Late cerebritis (days 4-9)
3. Early capsule formation (days 10-13)
4. Late capsule formation (day 14 and later).

Detailed histopathological examinations of the fully developed brain abscesses resulted in the characterisation of different zones from the centre to the periphery: 1) necrotic centre; 2) inflammatory cells, macrophages, and fibroblasts; 3) a dense collagenous capsule; 4) extensive vascularisation and cerebritis; 5) reactive astrocytes, gliosis, and cerebral oedema.

1.3. INCIDENCE

The incidence of brain abscess remains unclear and is suggested to range from 0.2 to 1.9 per 100,000 person-years[12-19]. The reasons for this uncertainty comprise different definitions of brain abscess, large variations in study periods, the scarcity of health care settings with access to high-quality nationwide and population-based data sources, difficulties in confirming the clinical diagnosis in some cases, and presumed low prioritisation within research communities. Thus, estimates of the occurrence of

brain abscess relies almost exclusively on historical single-centre reports of a limited number of patients from departments of neurosurgery with inherent selection and publication bias. At the onset of the studies included in this thesis, there were only a limited number of population-based cohort studies to document the incidence of brain abscess, of which two were nationwide (Table 1).

Based on previous literature, the incidence of brain abscess seems to have decreased during the last century due to improved care of chronic ear-nose-throat infections[16,20] along with decreases in the occurrence of severe head trauma[2,5] and in the prevalence of patients with congenital heart disease[21]. Concordantly, comparisons within and between different health-care settings also suggest that the incidence of brain abscess seems to decrease according to improvements in the overall socio-economic status of societies[14,22,23].

Table 1: Population-based observational studies of incidence of brain abscess.

Authors	Country	Study period	Setting	Number of patients	Patient identification	Incidence (100,000/year)
McClelland, 1978[12]	Northern Ireland	1947-1976	Single-centre, nationwide	172 (9 empyemas)	Record review at Dept. Neurosurgery + Centralised Autopsy Records registry	0.3
Svanteson, 1988[13]	Sweden	1947-1982	2 centres	151 (Non-traumatic, 4 empyemas)	Record review at Depts. Neurosurgery + Pathology	1.2
Nicolisi, 1991[14]	US	1935-1981	Single-centre	38 (13 empyemas)	Record review, Olmstead residents only	1.3
Helweg-Larsen, 2012[15]	Denmark	1994-2009	Single-centre	102	ICD-10 codes and record review at Depts. Neurosurgery, Neurology, and Infectious Diseases	0.4
Laulajainen-Hongisto, 2015[16]	Finland	1970-2012	Single-centre	166 (11 empyemas)	ICD-9 and 10 codes and record review at Dept. Neurosurgery	0.3
Bartek, 2016[17]	Sweden	2003-2014	Single-centre	40 (surgically treated)	Record review at Dept. Neurosurgery	0.2
Larsen, 2017[18]	Denmark	1995-2014	Single-centre	80 (surgically treated)	Record review Dept. Neurosurgery	0.3
Ter-Ong, 2017[19]	Taiwan	2000-2013	Insurance registry, nationwide	6,027	ICD-9 codes including intracranial empyema and intraspinal abscess	1.9 (no use of standardisation)

1.4. PATHOGENS

Brain abscess can be caused by bacteria, mycobacteria and branch-forming bacteria (nocardia and actinomyces spp.), fungi, and parasites. Historically, streptococcal and staphylococcal species have been the predominant pathogens[2,5]. This is confirmed in a large meta-analysis from 2014 comprising all published studies of brain abscess since 1970[10] and in unpublished data from the Danish Study Group of Infections of the Brain (DASGIB) of all Danish patients with brain abscess from 2007 through 2016 (Table 2). However, it appears that staphylococcal spp. have become less frequent in developed countries in recent decades[15,16].

Table 2: Causative pathogens of brain abscess.

	DASGIB*
Study period	2007-2016
Study population	All persons admitted in Denmark during the study period
Patients with positive culture/identification	345/444 (78)
Oral cavity bacteria (*e.g.* viridans streptococci, fusobacteria, anaerobic bacteria**)**	208 (47)
Other streptococcal spp.	
S. pneumoniae	10 (2)
Enterococci	6 (1)
Beta-haemolytic streptococci	5 (1)
Staphylococcus aureus	27 (6)
Skin-colonizing bacteria (Propionibacteria, coagulase-negative staphylococci, corynebacteria**)**	14 (3)
Gram-negative enteric (Proteus spp., klebsiella spp., *Escherichia coli***)**	12 (3)
Listeria monocytogenes	8 (2)
Pseudomonas spp.	4 (1)
Actinomycetales	15 (3)
Nocardia spp.	12 (3)
Actinomyces spp. (mono-culture)	2 (0.2)
Mycobacterium tuberculosis	1 (0.2)
Fungi	16 (4)
Parasites (*Toxoplasma gondii*)	11 (2)
Other	8

* Unpublished data from Danish Study Group of Infections of the Brain (DASGIB) obtained by medical record review of all Danish adults with an ICD-10 diagnosis code for brain abscess in the Danish National Patient Registry from 2007-2016.

Using state-of-the-art bacterial DNA sequencing from brain abscesses, studies have shown that almost all brain abscesses caused by oral cavity bacteria and those associated with ear-nose-throat infections are polymicrobial and include anaerobic bacteria[24-26]. Notable exceptions to these findings are brain abscesses caused by *S. aureus*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, or nocardial species. Fungal brain abscess is most often caused by aspergillus species[27] and parasitic brain abscess by *Toxoplasma gondii*[28,29]. The causative pathogen remained unknown in about one third of brain abscess patients in a large meta-analysis[10] although data in Table 2 suggest that this has decreased to approximately 23% in Denmark.

1.5. RISK FACTORS

Risk factors for brain abscess can be categorised according to pathogenic pathway and host conditions (Figure 2).

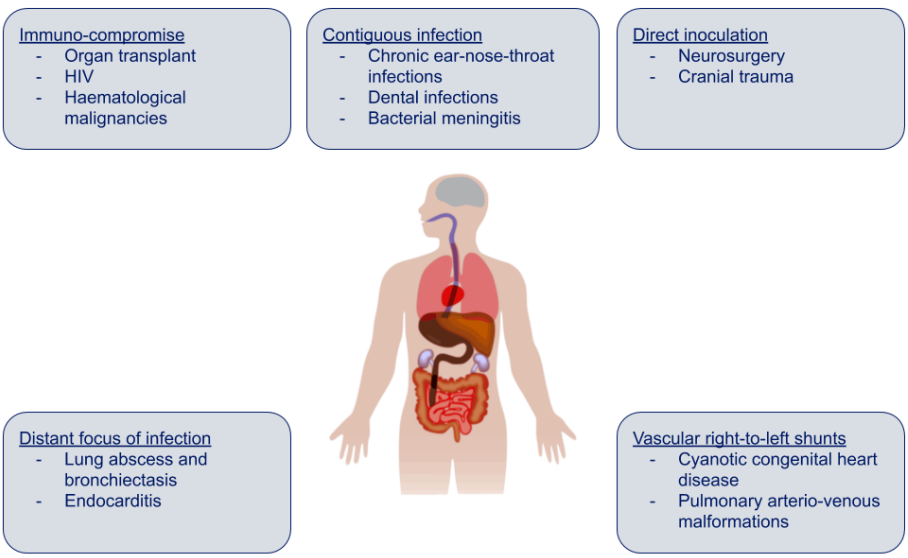


Figure 2: Risk factors for brain abscess in humans.

The relative importance of suggested risk factors varies between health-care settings and may be associated with certain pathogens. In less developed settings with limited

resources, predominant risk factors seem to be head trauma[5,22], chronic ear-nose-throat infections[5,6,20,22,23], Human Immunodeficiency Virus (HIV)[22], and cyanotic congenital heart disease[30,31]. This is in contrast to more developed countries, where previous neurosurgery, immuno-compromising conditions, and dental infections are significant risk factors[15,16,32].

Risk factors for brain abscess have predominantly been inferred by studies of patients admitted with brain abscess at departments of neurosurgery with inherent risks of selection bias. In addition, these studies were hampered by limited sample size and many examined more historical study populations. None of the studies were able to validate and quantify risk factors by comparisons with control populations or to estimate how much each risk factor contributes to the occurrence of brain abscess on a societal level (*i.e.* population attributable risks).

1.6. SYMPTOMS AND SIGNS

Symptoms and signs of brain abscess are often surprisingly modest and undramatic at admission. Headache is the most common symptom and occurs in 69% of patients, while fever is observed in 53% of patients[10]. Neurological deficits are present in 48% of patients and correlate with the anatomic localisation of the brain abscess and surrounding oedema. Other symptoms include nausea (47%), altered consciousness (43%), and seizures (25%). Only 20% of patients present with the classic triad of fever, headache, and focal neurological deficits[10]. Eventually, the abscess may rupture into the ventricles or onto the surface of the brain (2-35%)[33-37], causing immediate and serious deterioration of the patients' clinical condition and need for treatment at the intensive care unit. Rupture is often preceded by intense headache and syncope followed by meningeal reactions caused by the resultant subdural inflammatory response. Blood tests are usually unremarkable with normal levels of c-reactive protein observed in 40% of patients[10].

1.7. DIAGNOSIS

The diagnostic work-up for brain abscess includes cranial CT or magnetic resonance imaging (MRI), a neurosurgical procedure, and microbiological examinations of brain abscess material, blood, and other (contiguous or distant) foci of infection.

A tentative diagnosis of brain abscess is usually based upon the presence of a mass lesion on cranial CT or MRI in patients presenting to hospital with headache or a neurological deficit. MRI has been shown to be superior to CT in differentiating brain abscess from tumours, especially for mass lesions that are hyperintense on diffusion-

weight imaging (DWI) and hypodense on apparent diffusion coefficient (ADC) sequences. This combination yields a sensitivity and specificity of 96% each,[38] although the value of DWI in post-operative brain abscesses may be limited [39].

However, a definite diagnosis of brain abscess requires neurosurgical aspiration or excision of brain abscess material. Besides confirming the diagnosis, the procedure also provides essential information on causative pathogen(s) and their antibiograms in addition to therapeutic reduction of brain abscess volume. Microbiological examinations of abscess material consist of aerobic and anaerobic cultures[40,41] and may include bacterial DNA sequencing methods [24-26].

Blood cultures are positive in 28% of patients. CT of the thorax and abdomen are often valuable for diagnosis of a distant focus of infection or in patients at risk of fungal (aspergillosis) brain abscess[42]. Serological analyses are occasionally helpful, especially for diagnosis of CNS toxoplasmosis in persons with HIV[27,43]. Although lumbar puncture is contraindicated in patients with brain abscess due to risks of brain shift, the procedure is sometimes performed early during admission in everyday medical practice before the diagnosis of brain abscess is made[10,43,44]. The diagnostic yield of CSF cultures is limited with only 24-40% turning out positive, while clinical deterioration attributed to lumbar puncture has been observed in 2-7% of patients[10,44].

1.8. TREATMENT

Treatment of brain abscess is a multi-disciplinary endeavour involving infectious diseases specialists, neurosurgeons, neuroradiologists, and clinical microbiologists. Key interventions include a combined diagnostic and therapeutic neurosurgical procedure and high-dose antimicrobial therapy for 6-8 weeks[43].

Stereo-tactically guided aspiration of brain abscess is now the preferred surgical technique compared with excision. Obvious advantages include the less invasive nature and tissue sparing nature of the procedure as well as the ability to reach abscesses located in eloquent or hard-to-reach areas of the brain. Although vulnerable to selection and publication bias as well as confounding by indication, a systematic review of studies of brain abscess from 1990 through 2008 found that aspiration was associated with decreased mortality compared with excision (7% vs. 13%)[45]. Currently, excision is reserved for brain abscesses located superficially or in the posterior fossa, and for those caused by difficult-to-treat pathogens such as nocardia and fungi[43].

To date, no randomised controlled trials exist to guide antibiotic treatment of bacterial brain abscess. Current guidelines are mainly based on a combination of expert opinion and retrospective data from single neurosurgical centres. Historically, the preferred

empiric treatment regimens consisted of high-dose intravenous benzylpenicillin and chloramphenicol with the addition of metronidazole in the late 1970's[46]. This has since been replaced by a 3rd generation cephalosporin[47,48] combined with metronidazole in immuno-competent patients[20,43,49-52]. For immuno-compromised individuals or depending on exposures, the addition of trimethoprim-sulfamethoxazole (TMP-SMX), voriconazole, and anti-mycobacterial agents should be considered. For patients with recent neurosurgery or those at risk for methicillin-resistant *S. aureus* (MRSA) infection, vancomycin should be included.

1.9. PROGNOSIS

The prognosis of brain abscess has improved substantially since the remarkable and pioneering efforts of Sir William Macewen. Case fatality has decreased from 40-70% to 5-10% for community-acquired bacterial brain abscess in immuno-competent patients in recent decades[12-19,23], and seems only slightly higher in published studies from countries with more limited health-care resources,[22,53-55] although exceptions do exist[35,56,57] (Table 3). Of note, selection and publication bias may be particularly relevant in these settings. A few recent studies detailed standardised and complete follow-up with 1-year mortality rates of 11% and 19%[15,18]. Case fatality among patients with post-operative brain abscess has been reported to be 21%[58] with higher mortality in patients with difficult-to-treat pathogens or severe immuno-compromise[59-63]. Long-term sequelae include neurological deficits in approximately 30% of survivors[10].

Epilepsy has a substantial impact on patient's lives due to the nature and treatment of the disease[64] and has been reported to occur in approximately 15-72% of survivors of brain abscess (Table 4). The epileptic substrate is likely scar tissue within the brain parenchyma as a consequence of the infection – while the contribution of any neurosurgical procedure is unknown.

Recurrence of brain abscess has been reported to occur in 0-8% of patients in recent decades[15,23,65-68], and is likely associated with unresolved or irreversible predisposing conditions.

Similar to estimates of incidence and risk factors for brain abscess, studies on prognosis are mostly single-centre and of limited sample size. Generally, they lack complete long-term follow-up and fail to provide comparison cohorts to better detail the effect of brain abscess on the outcome.

Table 3: Mortality of brain abscess.

Authors	Country	Study period	Setting	Number of patients	Patient identification	Case fatality rate (%)
Brouwer, 2014[10]	-	1935-2012	Meta-analysis	9,699	Published studies	Decreased from 40 to 10
Population-based cohort studies						
McClelland, 1978[12]	Northern Ireland	1947-1976	Single-centre, nationwide	172 (9 empyemas)	Record review at Dept. Neurosurgery + Centralised Autopsy Records registry	70
Svanteson, 1988[13]	Sweden	1947-1982	2 centres	151 (Non-traumatic; 4 empyemas)	Record review at Depts. Neurosurgery + Pathology	17
Nicolisi, 1991[14]	US	1935-1981	Single-centre	38 (13 empyemas)	Record review, Olmstead residents only	38
Helweg-Larsen, 2012[15]	Denmark	1994-2009	Single-centre	102	ICD-10 codes and record review at Depts. Neurosurgery, Neurology, and Infectious Diseases	30-day: 11 90-day: 17 1-year: 19
Laulajainen-Hongisto, 2015[16]	Finland	1970-2012	Single-centre	166 (11 empyemas)	ICD-9 and 10 codes and record review at Dept. Neurosurgery	7
Bartek, 2016[17]	Sweden	2003-2014	Single-centre	41 (surgically treated)	Record review at Dept. Neurosurgery	2
Larsen, 2017[18]	Denmark	1995-2014	Single-centre	80 (surgically treated)	Record review Dept. Neurosurgery	90-day: 8 1-year: 11

Ter-Ong, 2017[19]	Taiwan	2000-2013	Insurance registry, nationwide	6,027	ICD-9 codes including intracranial empyema and intraspinal abscess	12
Cohort studies from resource-limited settings						
Joshi, 1998[53]	Nepal	1990-1996	Single-centre	57	Record review at Dept. Neurosurgery	14
Qureshi, 2002[56]	Pakistan	1987-1998	Single-centre	66	Record review at Dept. Neurosurgery	29
Sichizya, 2005[54]	South Africa	1993-2003	Single-centre	121 (surgically treated; Trauma 45%)	Record review at Dept. Neurosurgery	13
Nathoo, 2011[22]	South Africa	1983-2002	Single-centre	973 (Trauma 33%; HIV 6%)	Hospital database	13
Manzar, 2011[55]	Pakistan	2000-2008	Single-centre	53	Record review at Dept. Neurosurgery	11
Tunthanathip, 2015[35]	Thailand	1999-2013	Single-centre	114	Record review at Dept. Neurosurgery	6-month: 27
Ndubuisi, 2017[69]	Nigeria	2004-2014	Two centres	79 (HIV 6%)	Record review at Depts. Neurosurgery	19
Miniar, 2018[57]	Tunisia	1995-2014	Multi-centre	41 (children)	Medical record review	24

Table 4: Risk of epilepsy in patients with brain abscess.

Authors	Country	Study period	Setting	Number of patients	Available for follow-up	Patient identification	Epilepsy (%)
Population-based studies							
McClelland, 1978[12]	Northern Ireland	1947-1976	Single-centre	172 (9 empyemas)	52	Record review at Dept. Neurosurgery + Centralised Autopsy Records registry	19
Nicolisi, 1991[14]	US	1935-1981	Single-centre	38 (13 empyemas)	18	Record review, Olmstead residents only	28 Mean follow-up 15 years (range 1-45)
Laulajainen-Hongisto, 2015[16]	Finland	1970-2012	Single-centre	166 (11 empyemas)	154	ICD-9 and 10 codes and record review at Dept. Neurosurgery	20
Bartek, 2016[17]	Sweden	2003-2014	Single-centre	40 (surgically treated)	41	Record review at Dept. Neurosurgery	25
Other studies							
Northcroft, 1956[70]	England	1947-1955	Single-centre	100 (77 supratentorial)	45 (9 subdural empyemas)	Record review at Dept. Neurosurgery	47
Beller, 1973[71]	Israel, 1973	1941-1971	Single-centre	89	45	Record review at Dept. Neurosurgery and Dept. Pathology	15

Legg, 1973[72]	England	1939-1966	Single-centre	186	70	Record review at Dept. Neurosurgery	72 Mean follow-up 11 years (range 1-30)
Nielsen, 1983[73]	Denmark	1935-1976	Single-centre	200	67	Record review at Dept. Neurosurgery	55 Mean follow-up 18 years (range 3-40)
Koszewski, 1991[74]	Poland	1948-1988	Single-centre	108 (survivors only)	108	Record review at Dept. Neurosurgery	34 Mean follow-up 11 years (range 3-21)
Kilpatrick, 1997[75]	Australia	1984-1994	Single-centre	35	20 (10 died, 5 lost to follow-up)	Record review at Dept. Neurosurgery	35 Mean follow-up 2.6 years (range 0.04-9)
Chuang, 2010[34]	Taiwan	1986-2007	Single-centre	205 (excluded previous stroke/hypoxic brain injury/epilepsy, head trauma)	148 (43 died, 14 lost to follow-up)	Record review at Dept. Neurosurgery	23 Min. 1.5 years of observation. Did not account for competing risks.
Lee, 2018[67]	South Korea	2002-2016	Single-centre	119 (All supratentorial, excluded head trauma, previous neurosurgery, fungal brain abscess)	117 (2 died)	Record review at Dept. Neurosurgery	19 Follow-up in intervals, median 1.25 years (range 0.04-10.2)

1.10. AREAS OF UNCERTAINTY

The rarity of brain abscess has largely precluded the development of evidence-based treatment recommendations. Thus, numerous areas of uncertainty remain and should ideally be addressed in future large-scale international research collaborations. This includes the establishment of reliable and reproducible animal models, further investigations into the pathogenesis of brain abscess, and standardised pharmacokinetic studies of intra-cavitary penetration of oral and intravenous antibiotics. Moreover, comparative studies of different antibiotic regimens and treatment durations[32,48,76-78] as well as neurosurgical techniques[45] are important unanswered clinical questions. Although a few studies have examined the usefulness of continuous drainage and irrigation of brain abscess with or without intra-cavitary antibiotic treatment[3,79-81], such issues should also be explored further in animal studies and properly controlled clinical trials. Finally, unravelling the role of adjunctive dexamethasone[82-84] and anti-convulsive treatment[34,72,74,75] is of interest in order to improve medical care of this devastating disease.

CHAPTER 2. OBJECTIVES

The purpose of this thesis was to conduct studies of the incidence, risk factors, treatment, and long-term prognosis of brain abscess. Specific objectives of included studies were as follows:

Study I Anti-infective treatment of brain abscess. To review studies describing the anti-infective treatment of brain abscess including animal models, pharmacokinetic data, and clinical studies.

Study II Positive predictive (PPV) value of ICD-10 diagnosis codes for brain abscess in the Danish National Patient Registry. To examine the PPV of ICD-10 diagnosis codes for brain abscess in the Danish National Patient Registry from 2007 through 2016.

Study III Risk factors of brain abscess: a nationwide-population-based nested case-control study. To examine and quantify risk factors for brain abscess and estimate population-attributable fractions compared with matched population controls.

Study IV Incidence and mortality of brain abscess in Denmark: a nationwide population-based study. To examine temporal trends in the incidence of brain abscess in Denmark from 1982 through 2016 as well as 1-year mortality.

Study V Long-term mortality and epilepsy in patients after brain abscess. To examine the long-term mortality and cumulative incidence of epilepsy in patients with brain abscess compared with matched control cohorts.

CHAPTER 3. MATERIALS & METHODS

3.1. DATA SOURCES

Study I

The PubMed database is a public resource for biomedical literature managed free of charge by the United States National Library of Medicine. Other sources used were highly regarded textbooks of infectious diseases[51,52] and the database of a previously published systematic review and meta-analysis of studies on brain abscess between 1970 and 2013[10].

Studies II-V

The Danish Civil Registration System was established in 1968 as an administrative database to ease taxation and keep track of the Danish population[85,86]. The registry individually catalogued all persons living in Denmark (1968) and Greenland (1972), and since then every live born child and new inhabitants have been included as required by law[86]. At the time of this thesis, approximately 9.8 million persons have been cumulated in the registry[87] with more than 400 million person-years of observation and less than 0.3% of persons lost to follow-up[85].

The registry keeps track of the unique 10-digit Central Person Registration (CPR) number assigned to all Danish residents at birth or immigration (Figure 3).

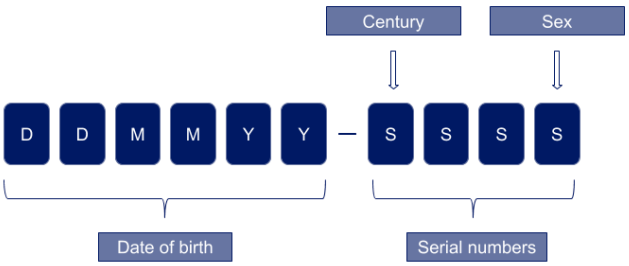


Figure 3: Elements of the Danish Central Person Registration (CPR) number.

The date of birth constitutes the first six digits and the remaining four numbers are used to distinguish persons born on the same date. Digits 5-7 indicate the year and century of birth, while the last number identifies the sex of the individual (even for

females; odd for males). This personal identifier cannot be used for any other individual in the future, even if the index person has died, emigrated, changed sex, or has been included into a witness protection programme[87].

Besides storing the names and CPR-numbers of all Danish residents, The Danish Civil Registration System also contains information on the vital and migration status on a day-to-day basis, address, citizenship, kinship (*i.e.* CPR numbers of parents, siblings, and children for all individuals born after 1952),[86] marital status, voting rights, and membership of the Evangelical Lutheran Church in Denmark[85,86].

The quality of the data in the registry is considered very high, because of its continuous use and validation by public institutions for contact with Danish residents including all health care services[86,88]. This allows for unambiguous linkage of information on individuals between registries (Figure 4).

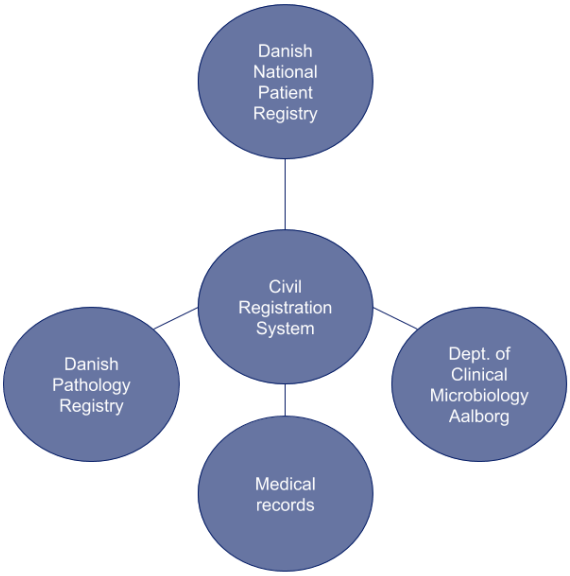


Figure 4: Data sources used for studies II-V.

The Danish National Patient Registry was founded in 1977 by the Danish Board of Health to keep track of the activity of Danish hospitals[89,90]. The registry holds information on all somatic hospital admissions since its establishment and was

expanded to include outpatient, psychiatric, and emergency department contacts since 1995.

For each patient contact, a primary diagnosis code and up to 20 secondary diagnosis codes is assigned by the attending physician and stored in the registry. This coding has been in accord with the World Health Organization's International Classification of Diseases (ICD) version 8 until 1994 when it was replaced by ICD-10. Likewise, surgical procedures have been notified to the registry using the Danish Classification of Surgical Procedures from 1977 through 1995 and by a Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures since then[89]. In addition to name, CPR number and diagnosis and procedure code(s) for each patient contact, the registry contains information on residence, department and hospital of admission, dates of admission and discharge, and admission type (acute versus non-acute)[89]. Certain in-hospital medical treatments such as chemotherapy and biological treatments have also been mandatorily included in the registry since 2001[89].

Although primarily intended as an administrative governmental database, the Danish National Patient Registry is increasingly being used for research[91]. An essential prerequisite for this purpose is a high validity and completeness of the included information, especially diagnosis codes. To this end, data sent to the registry from hospitals is automatically checked for missing (primary) codes, incorrect digits, erroneous CPR numbers, and discrepancies between diagnoses and sex (*e.g.* males cannot be assigned a diagnosis code of ovarian cancer)[89]. The Danish Board of Health have formally confirmed the quality of the registry at several occasions using medical record review as reference[89,92]. The positive predictive value of a large variety of medical diagnoses was found to be 81% at the three-digit level using either the primary or two secondary diagnosis codes[89]. In addition, by 2015 at least 114 studies had examined various codes and found PPVs ranging from <15% to 100%[89]. However, the majority of studies showed PPVs >80% including codes used to compute the Charlson Comorbidity Index score[89,93]. Nonetheless, researchers should critically assess the accuracy of diagnosis codes when using the registry for health-care research.

The Danish Pathology Registry contains all pathology reports in Denmark since 1997, but extends to 1970's and 1980's in the four centres with neurosurgical departments[94]. Pathological diagnoses contained in this registry are catalogued according to the Danish Systemized Nomenclature of Medicine (SNOMED) codes.

The electronic medical records at the Department of Clinical Microbiology, Aalborg University Hospital, is used in everyday clinical management of patients. Moreover, the system has been used for research purposes for a large prospective observational database on bacteraemia in North Denmark Region since 1992[95].

3.2. STUDY POPULATION

Brain abscess patients (n=1,384).
Patients with a first-time hospital diagnosis of brain abscess in the period 1982 through 2016 were identified in the Danish National Patient Registry. The date of admission for first-time hospitalisation for brain abscess was considered the index date. Patients with subdural empyema were excluded as were those with newly diagnosed central nervous system (CNS) tumour, intraspinal abscess, or spondylodiscitis within 90 days of admission for brain abscess.

Population comparison cohort for case-control study (n=13,839).
We used the Danish Civil Registration System and Danish National Patient Registry to randomly identify 10 persons for each case individually matched by age, sex, and municipality code on the index date. In addition, population controls had to be alive and without a brain abscess diagnosis code at time of matching. Population controls were allowed to serve as controls for several cases if selected as such by chance. Using this risk-set sampling approach, odds ratios can be considered equivalent to incidence rate ratios[96].

Population comparison cohort for cohort study (n=13,838).
We used the Danish Civil Registration System and Danish National Patient Registry to identify 10 persons for each case individually matched by age, sex, and municipality code on the index date. In addition, population controls had to be alive and without a diagnosis code for brain abscess at time of matching. Population controls could only serve as controls for one case each.

Appendicitis comparison cohort for cohort study (n=6,887).
We used the Danish Civil Registration System to identify all persons with a diagnosis of appendicitis within one month of the index date for each brain abscess patient. From this cohort, we randomly selected five appendicitis controls for each case individually matched by age (+/- 5 years) and sex on the index date (+/- 1 month). Appendicitis controls had to be alive and without a diagnosis code for brain abscess at time of matching. Finally, appendicitis controls could only serve as controls for one case each.

Siblings for cohort study (n=1,034 for cases and n=10,025 for controls).
Siblings of patients and population controls from the cohort study were identified using the Danish Civil Registration System.

3.3. STUDY DESIGNS AND OUTCOMES

Study designs in this thesis include a narrative review (Study I), a cross-sectional study (Study II), a case-control study (Study III), an open and closed unmatched cohort study (Study IV), and a closed matched cohort study (Study V).

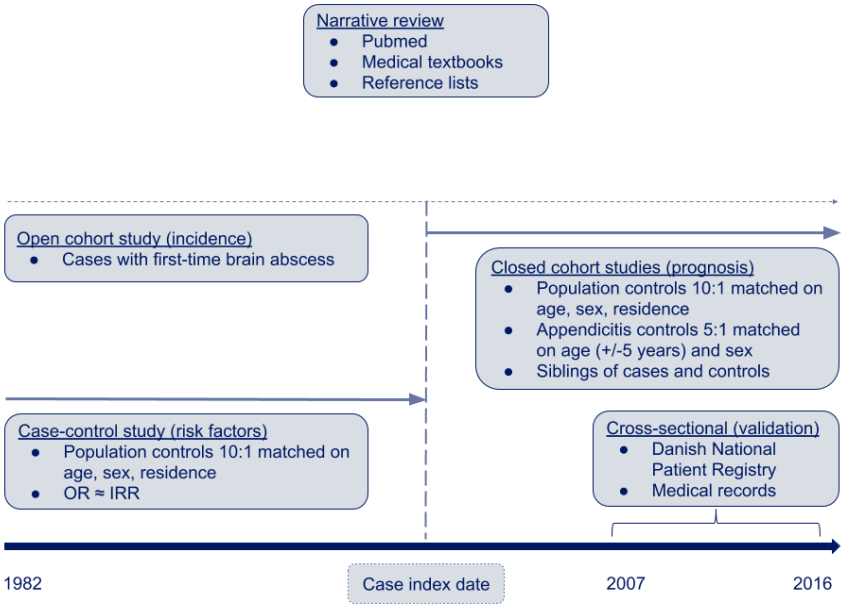


Figure 5: Study designs used in this thesis.

The primary outcome in each study were:

Study I Comprehensive summary of studies examining anti-infective treatment of brain abscess.

Study II The PPV of brain abscess diagnosis codes in the Danish National Patient Registry.

Study III Estimates of relative risks (*i.e.* odds ratios) of suggested known as well as novel risk factors and their population attributable fractions.

Study IV The incidence of brain abscess as well as 30-, 90-day, and 1-year mortality.

Study V Time from study inclusion to death and cumulative incidence of epilepsy in brain abscess patients compared with their matched population controls.

3.4. STATISTICAL ANALYSES

Estimates of incidence (Study IV)
Estimates of incidence of brain abscess were examined by direct standardisation using the Danish population in year 2016 as reference. Next, temporal changes were assessed by incidence rate ratios (IRR) with 95% confidence intervals (CI). A two-source capture-recapture analysis was conducted in North Denmark Region using the Danish National Patient Registry as the primary source and the electronic record system at the Department of Clinical Microbiology, Aalborg University Hospital as the secondary source. In a supplementary analysis, we also searched the Danish Pathology Registry for any missed cases.

Observation time (Studies III-V)
The index date was defined as first date of hospitalisation with brain abscess for patients as well as their matched population controls and sibling cohorts.

For the case-control study, all exposures from January 1, 1982 until the day before the index date were registered, except for head trauma, ear-nose-throat infections, and dental infections for which the index date was included.

For the cohort studies, we calculated the observation time from the index date to date of death, emigration, loss to follow-up, or January 1, 2017, whichever came first. However, for appendicitis controls we used the date of admission for appendicitis as the index date to compute observation time.

Kaplan-Meier survival analyses (Studies IV and V)
Survival was illustrated by Kaplan-Meier curves

Regression analyses (Studies III-V)
Crude and adjusted odds ratios for suggested risk factors of brain abscess were examined by conditional logistic regression. We used Cox regression analyses to compute unadjusted and adjusted mortality rate ratios (MRR) with 95% confidence intervals (CI). For all exposure variables, the proportional hazards assumptions were confirmed visually by log(-log(survival function)) against time.

Cumulative incidence function (Study V)
Cumulative incidence of epilepsy with 95% CIs was assessed by taking into account competing risks of death, emigration, and loss to follow-up.

CHAPTER 4. RESULTS

4.1. **STUDY I**

A search on studies of anti-infective treatment of brain abscess identified 546 articles in the PubMed database (Figure 6). Of these, the majority were excluded by title, abstract, or article content leaving 145 studies for further consideration. Next, additional studies were identified by a cited reference search and consultation of infectious diseases textbooks[51,52] as well as the database of a previously published systematic review and meta-analysis[10]. Since this was a narrative review combined with limitations imposed by the publisher on the number of references, we included 113 studies that we considered important for discussion in this review.

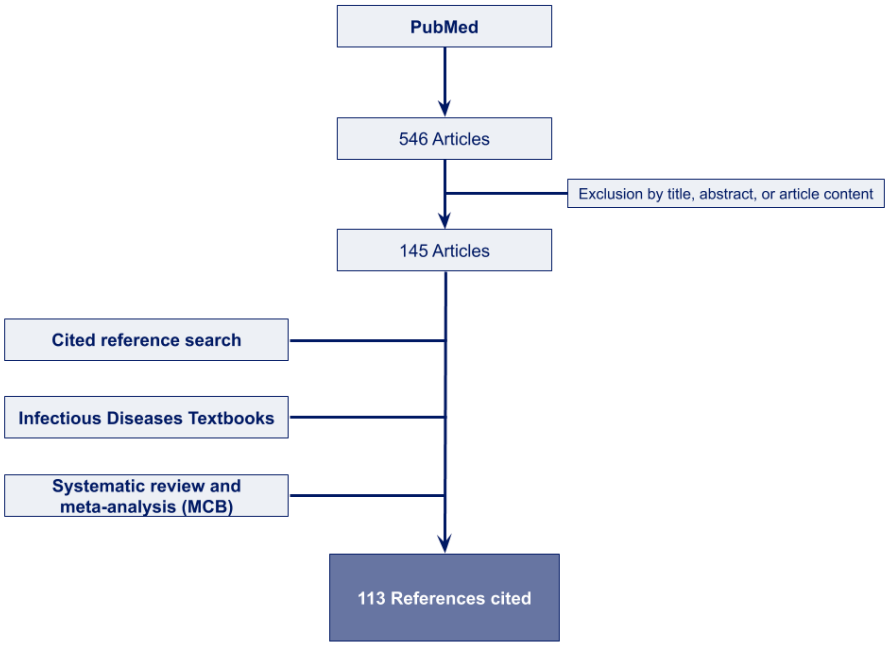


Figure 6: Literature search for narrative review on anti-infective treatment of brain abscess.

In general, animal models and clinical studies examining the anti-infective treatment of brain abscess are scarce. This applies for both choice of drugs, route and duration of therapy, as well as adjunctive treatments including dexamethasone. The existing

pharmaco-kinetic studies of intra-cavitary penetration of anti-infective drugs are mostly characterised by random *ad hoc* measurements in a limited number of patients early during treatment – mostly with drugs rarely used today. There are no randomised controlled trials of treatment of brain abscess.

Based upon the available literature to date, the suggested empirical and targeted anti-infective treatments are described in Table 5.

Table 5: Recommended anti-infective therapy for brain abscess. Adopted from Bodilsen J, Brouwer MC, Nielsen H, van de Beek D. Anti-infective treatment of brain abscess. Expert Rev Anti Infect Ther. 4 ed. 2018 Jul;16(7):565–78.

	Standard therapy	**Alternative therapies**
Empirical treatment		
Standard regimen	Cefotaxime* + metronidazole Consider adding vancomycin if MRSA is endemic or abscess is caused by previous neurosurgery or head trauma	Meropenem
HIV-positive patient	Add pyrimethamine and sulfadiazine to standard regimen	Pyrimethamine+clindamycin; TMP-SMX; pyrimethamine+azithromycin, clarithromycin, atovaquone or dapsone
Transplant recipients	Add voriconazole and TMP-SMX or sulfadiazine to standard regimen. Consider adding ampicillin for *L. monocytogenes.*	Liposomal amphotericin B, itraconazole, posaconazole
Targeted treatment		
Bacteria		
Actinomyces spp.	Penicillin G	Clindamycin
Bacteroides fragilis	Metronidazole	Clindamycin
Enterobacteriaceae	Cefotaxime	Meropenem, fluoroquinolone, TMP-SMX, aztreonam
Fusobacterium spp.	Metronidazole	Clindamycin, meropenem
Listeria monocytogenes	Ampicillin +/- gentamicin	TMP-SMX
Mycobacterium tuberculosis	Isoniazid, rifampin, pyrazinamide, ethambutol	

Nocardia spp.	Trimethoprim-sulfamethoxazole + imipenem Consider adding ceftriaxone in life-threatening or disseminated disease	Meropenem, third-generation cephalosporin, linezolid, moxifloxacin, amikacin, tigecycline, minocycline
Pseudomonas aeruginosa	Ceftazidime or meropenem +/- quinolone	Aztreonam, cefepime, tobramycin/gentamicin
S. aureus		
Penicillin-sensitive	Penicillin G	Vancomycin
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin
Methicillin-resistant	Vancomycin	TMP-SMX, linezolid, clindamycin, daptomycin
Fungi		
Aspergillus spp.	Voriconazole	Liposomal amphotericin B, itraconazole, posaconazole
Candida spp.	Liposomal amphotericin B +/- flucytosine	Fluconazole + flucytosine, voriconazole
Scedosporium spp.	Voriconazole	Itraconazole, posaconazole
Cryptococcus neoformans	Liposomal amphotericin B + flucytosine	Fluconazole, voriconazole, posaconazole
Mucorales	Liposomal amphotericin B	Posaconazole
Dematiaceous fungi	Liposomal amphotericin B + 5-FC +/- itraconazole/voriconazole/posaconazole	Itraconazole, voriconazole, posaconazole
Protozoa		
Toxoplasma gondii	Pyrimethamine + sulfadiazine	Pyrimethamine+clindamycin; TMP-SMX; pyrimethamine + azithromycin, clarithromycin, atovaquone or dapsone

4.2. STUDY II

We identified 709 patients with a primary or secondary diagnosis code for brain abscess in the Danish National Patient Registry from 2007 through 2016. Of these, the medical records could be retrieved for 694 patients and 444 were confirmed to have had a brain abscess.

Positive predictive value (PPV). The overall PPV of diagnosis codes for brain abscess was 64% (95% CI 60-68) and ranged from 24% to 96% between different diagnosis codes. However, the PPV increased to 84% (95% CI 80-87) by applying an algorithm in which patients were only included if:

1) They had a diagnosis and surgical procedure code for brain abscess

   Or

2) They had been admitted with a diagnosis code of DG060 (C, E, F) or DG079B without a newly diagnosed CNS cancer, spondylodiscitis or intraspinal abscess. In addition, these patients were omitted if they had a procedure code for intracranial empyema.

The algorithm successfully identified 89% (395/444) of patients with brain abscess confirmed by medical record review.

4.3. STUDY III

During the study period (1982-2016), we identified 1,384 brain abscess patients of which 37% were female and the median age was 50 years (interquartile range 33-63). In general, brain abscess patients had more comorbidity assessed by the Charlson Comorbidity Index score >2 than matched controls.

Adjusted odds ratios ranged from 2-20 for diabetes mellitus and previous neurosurgery, respectively (Figure 7).

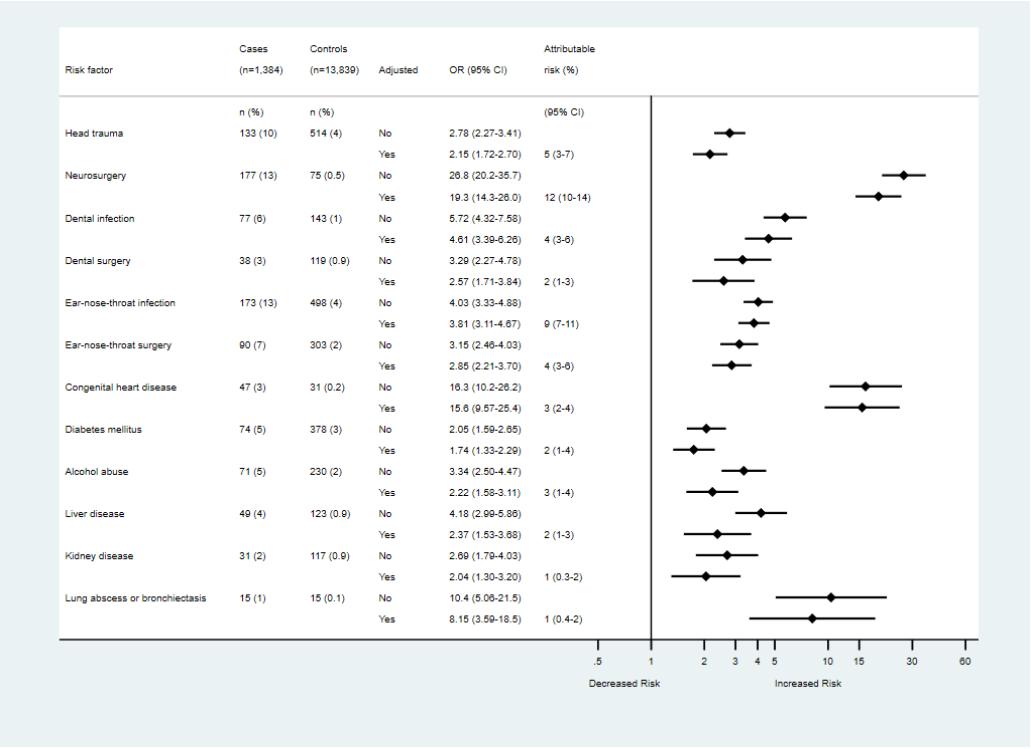


Figure 7: Risk factors for brain abscess and population attributable fractions. Adopted from Bodilsen J, Dalager-Pedersen M, van de Beek D, Brouwer MC, Nielsen H. Risk Factors for Brain Abscess: A Nationwide, Population-Based, Nested Case-Control Study. Clin Infect Dis. 2019 Oct 23;371:447–7.

The odds ratios were stable for all examined exposures throughout the study period, except ear-nose-throat infection for which the associated risk decreased in recent decades. Immuno-modulating treatments emerged as novel significant risk factors. Population attributable fractions suggested that neurosurgery (12%), solid cancer (11%), ear-nose-throat infections (7%), and immuno-modulating treatments (5%) were important risk factors on a societal level.

4.4. STUDY IV

In Denmark, we observed a steady increase in the incidence of brain abscess from 0.60 per 100,000 person-years during 1982-88 to 0.90 per 100,000 person-years during 2010-16 (Figure 8).

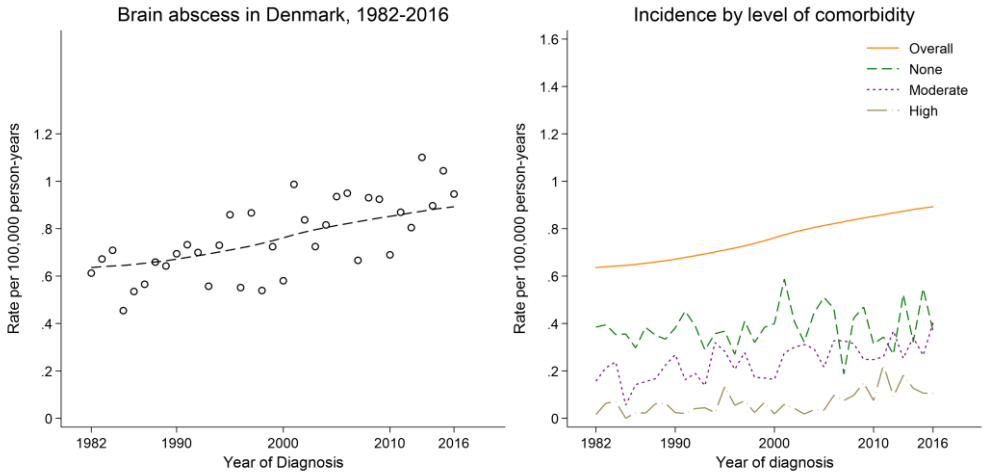


Figure 8: Incidence of brain abscess in Denmark from 1982 through 2016. Adopted from Bodilsen J, Dalager-Pedersen M, van de Beek D, Brouwer MC, Nielsen H. Incidence and mortality of brain abscess in Denmark: a nationwide population-based study. Clin Microbiol Infect. 2019 May 31;26(1):95–100

This was driven by a substantial increase in the incidence of brain abscess patients >40 years of age. We also observed an increase in the proportion of brain abscess patients with immuno-compromise. During the study period, we found a decrease in 1-year mortality from 29% to 20%, yielding an adjusted MRR of 0.44 (95% CI 0.31-0.63). Fatal outcome was associated with advanced age, Charlson Comorbidity Index score >0, immuno-compromise, and congenital heart disease.

4.5. STUDY V

We matched 1,384 brain abscess patients with 13,838 population controls and 6,887 appendicitis controls. Median follow-up was 5.9 years (interquartile range (IQR) 1.1-14.2), 11.2 (IQR 4.8-19.8) and 11.3 (IQR 4.8-20.0). There were no substantial differences between population and appendicitis controls and the latter were omitted from further analyses.

Mortality The observed 1-year, 2-5 year, and 6-30 year mortalities of brain abscess patients were 21%, 16%, and 27% versus 1%, 6%, and 20% for their matched population controls (Figure 9). The adjusted MRRs were 17.5 (95% CI 13.9-22.0), 2.61 (95% CI 2.16-3.16), and 1.94 (95% CI 1.62-2.31). Results remained consistent regardless of age group (except for patients >80 years of age), previous comorbidity or not, and immuno-compromise or not.

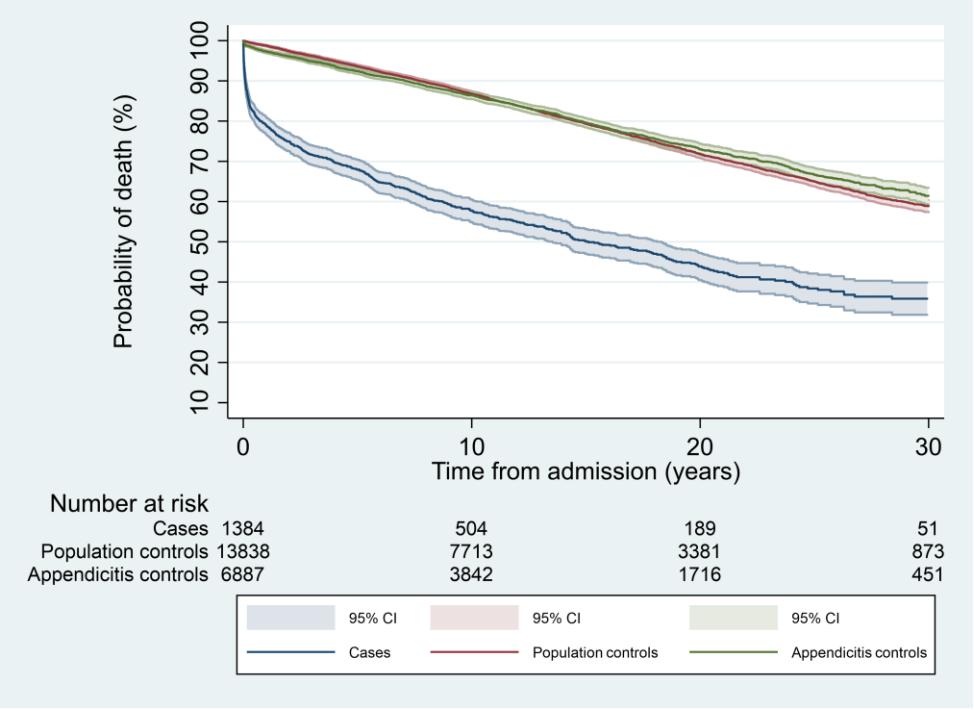


Figure 9: Mortality of brain abscess patients and their matched population controls. Adopted from Bodilsen J, Dalager-Pedersen M, van de Beek D, Brouwer MC, Nielsen H. Long-term mortality and epilepsy in patients after brain abscess: A nationwide population-based matched cohort study. Clinical Infectious Diseases. 2019 Nov 27.

Epilepsy Among 30-day survivors of brain abscess, the cumulative incidence of new-onset epilepsy was 32% versus 2% in matched population controls (Figure 10). The risk remained substantially increased beyond six years of observation.

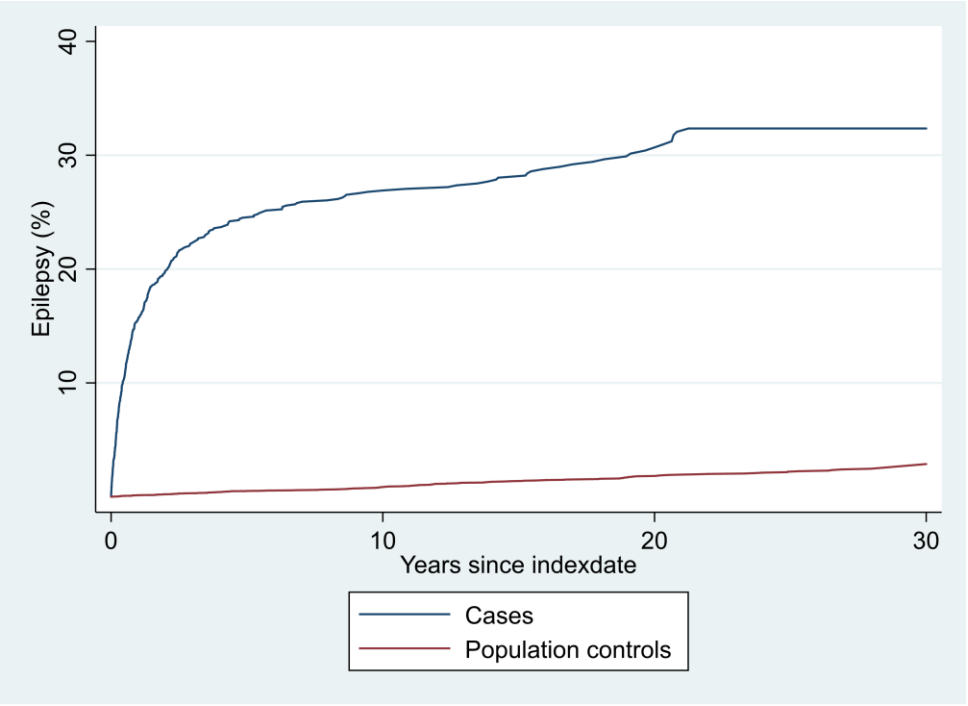


Figure 10: The cumulative incidence of epilepsy among brain abscess patients and their matched population controls. Adopted from Bodilsen J, Dalager-Pedersen M, van de Beek D, Brouwer MC, Nielsen H. Long-term mortality and epilepsy in patients after brain abscess: A nationwide population-based matched cohort study. Clinical Infectious Diseases. 2019 Nov 27.

Comparisons of sibling cohorts of cases and population controls showed that only a small fraction of the difference in risk of epilepsy could be explained by family-related factors.

CHAPTER 5. DISCUSSION

The primary aim of this thesis was to describe the treatment and epidemiology of brain abscess. Treatment was examined in a literature review and the epidemiological traits by studies that used public, nationwide, and population-based registries.

5.1. COMPARISONS WITH OTHER STUDIES

Study I This is the first comprehensive review to summarise existing animal studies, as well as pharmaco-kinetic and clinical studies on treatment of brain abscess. Recommendations are in line with most previously published guidelines and textbooks, [43,49,51,52] although some differences exist, *e.g.* on duration of intravenous therapy and the need for follow-up treatment with oral antibiotics[20,50]. Common to all guidelines, the recommendations are largely based upon expert opinion and observational studies, given the lack of randomised clinical trials and scarcity of standardised pharmaco-kinetic studies of brain abscess treatment.

Study II We have not been able to identify other studies examining the positive predictive value of ICD diagnosis codes in health care registries. In our study, the overall PPV (64%) of brain abscess diagnosis codes was poor to moderate. Erroneously coded hospital contacts were often seen among patients with CNS malignancy, intraspinal abscess and spondylodiscitis, or subdural empyemas. The results are vital for the conduct and interpretation of studies on brain abscess that rely upon ICD codes.

Study III This is the first case-control study of risk factors of brain abscess. Nonetheless, our results confirm and quantify most suggested risk factors such as neurosurgery, ear-nose-throat infections, and congenital heart disease from previously published case-only studies from tertiary care centres (Tables 3 and 4). Compared with historic reports[2,3,16,71], head trauma and chronic ear-nose-throat infections contribute less to the burden of this disease in our study. Using nationwide registries, we corroborate previous associations between risk of brain abscess and several immune-compromising conditions including organ transplant, HIV, and haematological malignancy[60-63]. We also show that numerous novel immuno-modulatory treatments are substantial risk factors for brain abscess.

Study IV We found a higher and increasing incidence of brain abscess (from 0.60 to 0.90 per 100,000 person-years) during the study period compared with recent population-based studies from similar health care settings (0.3-0.4 per 100,000 person-years; Table 1). Moreover, our results were confirmed by capture-recapture

analysis and supplemented by a search in a pathology register. In contrast to the only other nationwide population-based study using a large (insurance) registry in Taiwan, we applied a validated algorithm of diagnosis codes and excluded patients with intraspinal abscess[19].

Few studies of brain abscess have addressed mortality beyond case-fatality rates and most originate from single departments of neurosurgery. Importantly, we show that the mortality rate increases from 7% to 20% from 30 days to one year after admission for brain abscess. This is in line with findings from a few other existing studies reporting 1-year mortality[15,18].

Study V Previous studies on long-term mortality and risk of epilepsy after brain abscess are almost entirely of single-centre, historic patient cohorts with limited sample size and incomplete follow-up (Tables 3 and 4). No other studies have formally examined mortality beyond the first year since diagnosis and none included population controls for comparison of risk.

We observed for the first time, that patients continue to have an increased risk of death for up to 30 years since diagnosis of brain abscess compared with their matched population controls. Using our large, contemporary cohort of brain abscess patients and accounting for competing risks, we also showed that the cumulative incidence of epilepsy is approximately 32% in these patients. Although one study has suggested a risk of epilepsy of 72% in brain abscess patients treated between 1939 and 1966, our results are consistent with most other single-centre and population-based studies (Table 4).

5.2. METHODOLOGICAL CONSIDERATIONS

Systematic and random error (chance) must be considered when assessing the internal validity of any observational study and suggestions of causality[97]. Systematic error is often categorised as selection bias, information bias, and confounding, while random error refers to the statistical accuracy of estimates[97,98].

5.2.1. SELECTION BIAS

Selection bias is defined as systematic error related to the way study participants are included or factors that influence study participation[97,98]. The bias is important when observed associations between exposure and outcome differ considerably between study participants and non-participants. However, such differences are almost always unknown and selection bias should be inferred[97].

Study I was conducted as a comprehensive narrative review and although great effort was made to include all relevant studies on the topic, a formal protocol for a systematic review was not applied. Moreover, the review is vulnerable to publication bias as well as the subjective assessment of importance by the authors. Nonetheless, we provided the terms used for our search in the United States National Library of Medicine (Pubmed) and accessed the database of a previous systematic review of published studies on brain abscess from 1970 until 2013[10].

Study II is a cross-sectional study and may as such be vulnerable to selection bias if the study population is not representative of the background population. However, the Danish welfare system with tax-financed health care for all residents combined with the use of nationwide and population-based databases consisting of routinely collected information during every day clinical practice (*i.e.* the Danish National Patient Registry and electronic medical records), substantially reduces the risk of selection bias.

All control populations for **studies III and V** were randomly selected using certain matching criteria from the Danish Civil Registration System, which encompasses the entire Danish population with less than 0.3% loss to follow-up[85]. This makes bias owing to the sampling procedures of controls and loss to follow-up virtually non-existent.

Study III was a case-control study and selection bias may be present if study inclusion of cases and controls depended on exposure status. Brain abscess patients were often more comorbid than their matched controls and hospital contacts are likely to be more frequent, whereby further comorbidities are diagnosed. Moreover, the diagnostic threshold is probably lower for these patients compared with persons without comorbidity, which could lead to selection bias. However, brain abscess is a fatal infection if left untreated and symptoms will progress until hospitalization or death. Thus, we consider any substantial differences in these events between cases and controls as very improbable.

Study IV used an open (incidence part) and closed (1-year mortality) cohort design and patient inclusion depended upon the accuracy and completeness of brain abscess diagnosis codes. We used a validated algorithm of diagnosis codes for identifying brain abscess patients (Study II) in a nationwide register including all hospitals in Denmark. In addition, a capture-recapture analysis showed that incompleteness of brain abscess diagnosis codes did not significantly change incidence rates. The study period also spanned more than three decades and increased use of cranial imaging[99] and refined neurosurgical techniques[7] may have contributed to increasing estimates of incidence. Still, a potential underestimation of the incidence of brain abscess during the beginning of the study period would only contribute to the overall conclusion that brain abscess is more frequent than previously believed.

For mortality rates, selection bias would be a serious concern if the association between the exposure (*i.e.* brain abscess) and the outcome (*i.e.* death) differed between study participants and non-participants, or in case of loss to follow-up. The negligible loss to follow-up in the Danish Civil Registration System has been mentioned previously. Importantly, we cannot rule out that the examined mortality rates of brain abscess patients not assigned a brain abscess diagnosis code or not included by our algorithm may differ from that of patients included in our study. To examine this further, we searched the Danish Pathology Registry in North Denmark Region and found only a few additional patients diagnosed with brain abscess at autopsy. Nonetheless, this may result in a slight underestimation of mortality rates.

Study V is a matched cohort study and selection bias may substantially affect results if the association between exposure status (*i.e.* brain abscess) and outcomes (*i.e.* death, epilepsy) or loss to follow-up differed between study participants and non-participants. Again, the completeness of the Danish Civil Registration System practically excludes loss to follow-up and ensures unbiased registrations of mortality. For estimates of epilepsy, selection bias may influence the results if the occurrence of seizures differed between brain abscess patients included in our study compared with persons with brain abscess that remain undetected or were not included by our diagnosis code algorithm. Although our capture-recapture analysis and subsequent search in the Danish Pathology Registry yielded only a very limited of patients not identified by the Danish National Patient Registry, we cannot entirely exclude that some selection bias may have led to an overestimation in the cumulative incidence of epilepsy among brain abscess patients.

5.2.2. INFORMATION BIAS

Information bias includes misclassification of exposure, outcome or variables on potential confounders[97]. Non-differential misclassification denotes misclassification that is entirely independent of comparison groups whereas differential misclassification is present when misclassification differs between groups. If variables are dichotomous, non-differential misclassification will most often result in bias towards unity as opposed to differential misclassification where the direction and magnitude of bias is difficult to predict[97].

Study I A large degree of heterogeneity existed between studies including (lack of) definitions of clinical characteristics, measurements of antimicrobial concentrations, and outcomes. Moreover, studies rarely provided data on the outcome of treatment at the individual level. This hampers both comparisons and aggregation of data and often precludes firm conclusions on the optimal antibiotic regimen.

Study II We accessed the medical records of patients registered with brain abscess in the Danish National Patient Registry to examine the PPV of brain abscess diagnosis codes. Since all information in the medical records is entered prospectively on a day-to-day basis by clinicians independent of future research projects, any misclassification of data between patients with confirmed or disproven brain abscess is likely non-differential and would thereby lead to conservative estimates of PPV. Similar considerations also apply for missing data, non-response bias, and recall bias. Moreover, we applied an *a priori* definition of brain abscess using variables readily available in the medical records in order to limit ascertainment bias, *i.e.* an assessor may be more willing to categorise patients with confirmed rather than disproven brain abscess in cases of doubt. This was also reflected by the distributions of definite (n=389), probable (n=41), and possible (n=14) brain abscess among the 444 patients with confirmed brain abscess.

Studies III-V Misclassification of brain abscess, exposures, outcomes, or confounder data may have influenced the results of our registry-based studies. However, we used a validated algorithm to identify brain abscess patients and all information for cases and controls was retrieved in the same way using the same nationwide sources with virtually complete follow-up (Danish Civil Registration System)[85,86] and high PPVs (Danish National Patient Registry)[89,93]. This reduces the impact of information bias and we expect most misclassification to be non-differentially distributed among cases and controls thereby driving estimates of relative risk towards the null.

Nevertheless, some differential misclassification may be present in the case-control study. Including the index date in analyses of risk factors will often result in an overestimation of measures of relative risk (*i.e.* odds ratios) for cases versus controls, because the latter are unlikely to be hospitalised on the index date. Thus, controls cannot be assigned a hospital diagnosis of the examined risk factor in contrast to cases that are likely to receive a thorough diagnostic work-up during admission. Conversely, not including the index date may result in an underestimation of risk factors among cases.

We tried to balance these two approaches by including the index date for short-term medical conditions with an immediate temporal risk of brain abscess (*e.g.* direct extension of ear-nose-throat infections) and not including the index date for more chronic conditions (*e.g.* diabetes mellitus, cancer or other immuno-compromising conditions), which may be undiagnosed in population controls at time of comparison.

Similarly, estimates of epilepsy may also be subject to differential misclassification since the threshold for assignment of such a hospital diagnosis is likely lower for brain abscess patients than in their corresponding population controls. This could lead to an overestimation of the cumulative incidence of epilepsy in brain abscess patients compared with population controls. Yet, the overall PPV of diagnosis codes for epilepsy has previously been shown to be 89%[100] and the incidence in the background

population (controls) is consistent with previous publications on the incidence of epilepsy in Denmark[101].

Finally, brain abscess patients were more comorbid prior to the index date than population controls, which is associated with frequent hospital contacts and even more complete coding of comorbidity. Such differential misclassification may potentially lead to both overestimation (*i.e.* surveillance bias) and underestimation of the impact of comorbidity on associations between brain abscess and risk factors or outcomes. Nonetheless, and as described previously, the PPV of the Danish National Patient Registry is generally very high[89], and we consider this potential influence to be minimal.

5.2.3. CONFOUNDING

Confounding is a systematic error that occurs when an association between exposure and outcome is confused with or distorted by the effect of a third (confounding) factor[97]. The definition also requires the confounder to be associated with the exposure and outcome without being an intermediate link in the chain of causation between exposure and outcome[97].

Studies III-V Although we controlled for confounding by matching, stratification, and multivariate analyses, some residual and/or unmeasured confounding is likely to remain. Importantly, we did not have access to clinical data such as smoking status, overall dental hygiene, functional status, or clinical parameters including microbiological aetiology. Other examples of possible residual confounding include crude matching or categorisations of confounders, which may result in loss of information. On the other hand, we were able to match population comparison cohorts by age, sex, and municipality code, with the latter serving as a proxy for socio-economic status. We also adjusted for several comorbidities in our analyses, thereby partly accounting for some of these potential confounders. Yet, unmeasured confounding may also have been introduced by adjusting for known confounders[97].

Other studies examining mortality of brain abscess have often identified clinical parameters such as abscess characteristics or intraventricular rupture of brain abscess as risk factors for death[22,32,65,102-104]. Although we acknowledge that such data are indeed of clinical importance, they often constitute part of the causal pathway leading from brain abscess to mortality, precluding them for use as confounding factors in adjusted analyses.

5.2.4. PRECISION

For the results of studies II-V, we consistently provided point estimates with 95% CIs to account for random error (chance). This reporting carries a quantitative strength indicating both the magnitude and statistical precision of observed associations in contrast to simple dichotomous significance testing (with associated p-values). This approach has also been endorsed by most biostatistical authorities and journals [97,105-107].

The large sample size in studies II-V yielded statistically precise estimates with narrow 95% CIs for the primary objectives and for most subgroup analyses. Yet, sparse data still precluded detailed adjusted analyses in some strata (*e.g.* certain age groups and those with predisposing congenital heart disease).

5.2.5. EXTERNAL VALIDITY

Our studies were conducted within a tax-financed welfare state with unrestricted access to health care free at the point of delivery. This may reduce the generalisability of our results to other settings with more limited health care resources. However, as the aetiology, clinical presentation, treatment, and outcome of brain abscess is fairly homogenous across continents, we find it likely that our results are applicable to most other settings with comparable health care systems and infrastructure.

CHAPTER 6. CLINICAL IMPLICATIONS AND PERSPECTIVES

This thesis highlights some of the challenges in the treatment of brain abscess and extends our existing knowledge on the incidence, risk factors, and prognosis of brain abscess.

Our review of anti-infective treatment of brain abscess confirms that empirical therapy of community-acquired brain abscess in immuno-competent individuals should consist of a 3rd generation cephalosporin and metronidazole. Importantly, there are no randomised controlled trials to inform physicians on the optimal choice of anti-infective drugs, and recommendations are largely based upon expert opinion and observational studies from tertiary care centres. Furthermore, the review emphasises the need for standardised pharmaco-kinetic studies of the intra-cavitary penetration of modern anti-infective drugs. Besides examining ratios of 'area under the curve' (AUC) between blood and pus, such studies should also address drug accumulation during treatment and the potential for early transition to oral antibiotics. Moreover, further clarification of the role of the blood-brain-barrier during early and late stages of brain abscess treatment is warranted.

Nationwide and population-based health care registries in Denmark and other Scandinavian countries provide researchers with a unique and invaluable opportunity to examine both common and uncommon diseases on a large scale at a fraction of the cost and time spent if such data were to be acquired from clinical studies or databases. This is possible due to 1) the provision of universal health care by the welfare state, 2) the possibility of individual linkage, and 3) a long tradition of longitudinal routine data collection[108]. At the same time, inherent risks of registry-based studies with large sample sizes include spurious associations without biological or clinical relevance[109]. Besides keeping such caveats in mind, careful evaluation of codes used also remains crucial as illustrated by the required algorithm to improve the PPV of brain abscess diagnosis codes in our validation study. Importantly, the study also showed that only 54% of brain abscess patients were assigned a diagnosis and procedure code for brain abscess at a neurosurgical department, which emphasises possible selection bias in studies relying on ICD-10 codes for patient inclusion at selected hospital departments. Thus, further clinical studies are needed to improve our knowledge on the clinical presentation and outcome of all brain abscess patients.

Our case-control study provides evidence of numerous risk factors for brain abscess supplemented by measures of importance on a societal level (*i.e.* population attributable fractions). These findings combined with the increasing incidence of brain abscess are important for clinicians and serve as an encouragement to maintain a low

threshold for performing a diagnostic work-up for this condition in vulnerable patient groups. In addition to a continued search for methods to improve preventive care, further characterisations of certain risk factors such as specific neurosurgical procedures, dental infections, or severity of immuno-compromise would be helpful to optimise patient care. Still, some questions remain unanswered. The relatively large proportion of patients with cryptogenic brain abscess (≈20%) and continued predominance of oral cavity bacteria as pathogens underlines the need for further scientific investigations into the pathogenesis of brain abscess that ultimately could help shed light on new ways to decrease the burden of this serious infection.

Although we observed that both 30-day and 1-year mortalities have halved among brain abscess patients during recent decades, the 1-year mortality remains substantial at ≈20%. Moreover, brain abscess patients have a continued increased mortality for up to 30 years compared with the background population and almost one third of patients develop epilepsy during their lifetime. This is of considerable concern for clinicians and public health authorities and constitutes a major incentive to improve immediate as well as long-term clinical management of brain abscess patients. A prerequisite for such improvement should be the implementation of a specialised multi-disciplinary team of neurosurgeons, infectious diseases specialists, neurologist, and microbiologists at all centres treating these patients. Furthermore, large international collaborations are needed to examine promising new therapies including early transition to oral antibiotics and well-known surgical principles of abscess treatment such as continued drainage, irrigation, and intra-cavitary anti-infective treatment.

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